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EXAMINER	
FALK, ANNE MARIE	

ART UNIT	PAPER NUMBER
1632	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

SIP_Docket@mwe.com

Office Action Summary	Application No.	Applicant(s)	
	09/876,187	LIPTON ET AL.	
	Examiner	Art Unit	
	Anne-Marie Falk, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 November 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *80-99* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *80-99* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *18 March 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The amendment filed November 12, 2009 (hereinafter referred to as "the response") has been entered. Claims 1-20 and 58-79 have been cancelled and Claim 80 has been amended. Applicants elected the species of *in vitro*.

Accordingly, Claims 80-99 remain pending in the instant application.

The rejection of Claims 1, 2, 18, 58-60, 76, and 79-99 under 35 U.S.C. 102(b), as being anticipated by Skerjanc et al. (4/21/2000, FEBS Letters 472(1): 53-63), as evidenced by Skerjanc et al. (1998, J. Biol. Chem. 273(52): 34904-34910), is **withdrawn** in view of the cancellation of Claims 1, 2, 18, 58-60, 76, and 79 and further in view of the arguments presented at pages 16-17 of the response, wherein Applicants assert that the plasmid construct of Skerjanc et al. encodes the wild-type MEF2C polypeptide rather than a constitutively active MEF2 polypeptide or an active fragment thereof, as set forth in the present claims. Applicants point to the definition of "constitutively active" at page 40 of the specification.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114 was filed in this application after appeal to the Board of Patent Appeals and Interferences, but prior to a decision on the appeal. Since this application is eligible for continued examination under 37 CFR 1.114 and the fee set forth in 37 CFR 1.17(e) has been timely paid, the appeal has been withdrawn pursuant to 37 CFR 1.114 and prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on November 12, 2009 has been entered.

Priority

Applicant's claim for domestic priority under 35 U.S.C. 119(e) is acknowledged. However, the provisional application upon which priority is claimed fails to provide adequate support under 35 U.S.C. 112 for Claims 80-99 of this application, for the same reasons discussed hereinbelow as applied to the present application. Application serial no. 60/209,539 fails to provide an enabling disclosure for the invention now being claimed in Claims 1-20 and 58-99, for the reasons discussed herein below as a rejection under 35 U.S.C. 112, first paragraph, as applied to the instant application.

Thus, the earlier-filed application does not meet the requirements under 35 U.S.C. 119(e) for the benefit of obtaining priority to an earlier-filed application, as the earlier-filed application does not enable the full scope of the presently claimed invention.

At page 5 of the response, Applicants refer to their position of record and the arguments presented in the present response. The arguments of record have already been addressed in the prior Office actions.

Applicants' arguments regarding the enablement rejection are addressed in detail below and were found to be only partially persuasive. Accordingly, the earlier-filed application does not meet the requirements under 35 U.S.C. 119(e) for the benefit of obtaining priority to an earlier-filed application, as the earlier-filed application does not enable the full scope of the presently claimed invention, for the same reasons discussed hereinbelow.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 80-99 stand rejected under 35 U.S.C. 112, first paragraph, for reasons of record advanced in the Office Actions of 6/16/04, 11/29/04, 8/12/05, 1/19/07, 1/2/08, and 3/18/09, as modified below, and for the reasons discussed herein, because the specification, while being enabling for

a method of differentiating progenitor cells *in vitro*, comprising the steps of (a) contacting *in vitro* said progenitor cells with retinoic acid; and (b) introducing *in vitro* into said progenitor cells a nucleic acid molecule encoding a constitutively active MEF2C polypeptide, wherein said progenitor cell is selected from the group consisting of a P19 cell and a mouse embryonic stem cell, thereby differentiating said progenitor cells to produce a cell population containing neuronal cells protected from apoptotic cell death,

does not reasonably provide enablement for the full scope of the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, are set forth in *In re Wands*, 8 USPQ2d 1400, at 1404 (CAFC 1988). These factors include: (1) the nature of the invention, (2) the state of the prior art, (3) the relative level of skill of those in the art, (4) the predictability of the art, (5) the breadth of the claims, (6) the amount of direction or guidance presented, (7) the presence or absence of working examples, and (8) the quantity of experimentation necessary (MPEP 2164.01(a)).

The following factors have been considered.

Nature of the invention and scope of the claims. The claims are directed to a method of differentiating progenitor cells, particularly embryonic stem cells and hematopoietic stem cells. The claims are now limited to *in vitro* applications of the method. The claims cover a wide variety of different types of stem cells and progenitor cells that could be used as the starting material. The specification asserts that the cell compositions developed from the claimed method are useful in therapeutic

transplantation. The claims are broad in scope and cover the use of any differentiating agent in combination with any progenitor cell, as well as a wide variety of MEF2 polypeptides encoded by the nucleic acid. Consequently, the method covers the production of a very large variety of heterogeneous cell compositions that comprise protected neuronal cells.

Amount of direction or guidance presented and the presence or absence of working examples. The examples of the specification are limited to producing a cell composition from a mouse embryonal carcinoma cell line (P19 cells) transfected with an MEF2 nucleic acid molecule or mouse ES cell line (D3 cells) transfected with an MEF2 nucleic acid molecule. Cells expressing MEF2C exhibited a bipolar cell phenotype that expresses both neuronal (neurofilament) and myogenic (myosin heavy chain) markers (specification at page 68, paragraph 2). All experiments were *in vitro* assays. The specification teaches that the cell compositions produced from the claimed method can be used to treat a wide variety of neurodegenerative diseases, including Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, Alzheimer's disease and other forms of dementia, multiple sclerosis, epilepsy, and pain (pages 1-3). With regard to the directed differentiation of human hematopoietic stem cells (HSCs) and human embryonic stem (ES) cells, as well as the transduction of these cell types, the specification provides only general guidance rather than specific guidance. Methods for the directed differentiation and genetic modification of human HSCs and ES cells were not known at the time of the instant invention. Therefore, considerable guidance is needed.

State of the prior art and predictability of the art. The specification fails to provide an enabling disclosure for the wide variety of progenitor cell types that may be used as the starting material. At the time the invention was made, successful implementation of directed differentiation protocols using stem or progenitor cells was not routinely achievable by those skilled in the art.

Regarding gene transfere into human HSCs, even as late as 2001, the art acknowledged that gene transfer into human hematopoietic stem cells was problematic (Hanazono et al., 2001). The claimed

invention must be enabled at the time of filing. However, the priority date of this application is June 5, 2000. Thus, the instant specification must provide an enabling disclosure for the claimed invention as of this priority date.

The specification fails to provide an enabling disclosure for the genetic modification of human ES cells. The recent literature addresses the difficulties encountered in attempting to transfect human ES cells. Zwaka et al. (2003) points out that there are significant differences between mouse and human ES cells and that "[h]igh, stable transfection efficiencies in human ES cells have been difficult to achieve, and, in particular, electroporation protocols established for mouse ES cells work poorly in human ES cells" (abstract). Thus, it is clear that the behavior of mouse ES cells is not predictive of human ES cells. In April 2001, Eiges et al. compared the efficiency of several different transfection protocols for human ES cells. The reference demonstrates use of the transfection protocol of ExGen 500 to transfect human ES cells. However, the instant specification does not provide specific guidance for transfecting human ES cells. Thus, at the time of filing, methods for successfully transfecting human ES cells were not known. The teachings of Eiges et al. (2001) would not have been available to the skilled artisan as of the claimed priority date of this application which is June 5, 2000.

The specification contemplates that transfecting the ES cells with a nucleic acid encoding an MEF2 and contacting the cells with a differentiating agent will be sufficient to direct the cells to differentiate *in vitro* into the appropriate cell type and functionally integrate into the tissue into which they are implanted. While much work has been done to develop techniques for the directed differentiation of mouse ES cells *in vitro* to produce desired cell types, little is known about the behavior of human ES cells under varied culture conditions.

The court has recognized that physiological activity is unpredictable. *In re Fisher*, 166 USPQ 18 (CCPA 1970). In cases involving unpredictable factors, such as most chemical reactions and

physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved. *In re Fisher*, 166 USPQ 18 (CCPA 1970).

Given the lack of applicable working examples, the limited guidance provided in the specification, the broad scope of the claims with regard to the wide variety of stem or progenitor cell types that could be used and the wide variety of cell compositions that may be developed from the claimed method, and the unpredictability for producing a cell population containing neuronal cells protected from apoptotic cell death, undue experimentation would have been required for one skilled in the art to practice the claimed method of the invention over the full scope.

At pages 6-7 of the response, Applicants submit that the specification fully satisfies the enablement requirement. Applicants note, citing *In re Buchner* (CAFC 1991), that a specification need not describe – and best omits – that which is well known in the art. Applicants further note that the enablement requirement is met if a preponderance of the evidence indicates that it is more likely than not that any person skilled in the art at the time the application was filed could have practiced the claimed methods. At page 7 of the response, Applicants note that a variety of methods are known in the art for introducing a nucleic acid into progenitor cells *in vitro*. Applicants cite pages 54-55 of the instant application and pages 27-28 of the provisional application for these teachings. However, the guidance provided in the specification is in the form of general guidance rather than specific guidance. Given that the state of the art in June 2000 was such that no one had successfully transfected human ES cells, it cannot be said that methods for transfecting human ES cells were known in the art. When methods for the genetic modification of human embryonic stem cells are not known in the prior art, specific guidance is needed to enable the invention. However, the instant specification provides no specific guidance with regard to the genetic modification of human ES cells. Zwaka et al. (2003) was first cited by the Examiner in the rejection of record in the Office Action of 11/28/03 for documenting the difficulties encountered in

attempting to transfect human ES cells. Zwaka et al. (2003) is a post-filing reference that describes an improved electroporation method that was specially adapted for human ES cells and the instant specification does not provide specific guidance for using electroporation techniques specially adapted for transfecting human ES cells. With regard to embryonic stem cells in general, the specification provides only a laundry list of techniques that could be used to introduce a nucleic acid molecule into an embryonic stem cell. With regard to human ES cells specifically, no specific guidance for their genetic modification is provided.

At page 8 of the response, Applicants point to the instant specification at page 55, lines 1-10 for teaching the use of viral vectors for introducing a nucleic acid molecule in the methods of the invention. Applicants conclude that the specification therefore teaches detailed methods for contacting in vitro progenitor cells with a differentiating agent and introducing in vitro into the progenitor cells a nucleic acid molecule encoding a constitutively active MEF2 polypeptide or an active fragment thereof. Again, however, with regard to transfecting human embryonic stem cells and human hematopoietic stem cells, the guidance provided in the specification is in the form of general guidance rather than specific guidance.

At page 8 of the response, Applicants point to the various references cited in the rejection of record in support of the Office's allegation that the specification fails to provide an enabling disclosure for the therapeutic use of the cell compositions produced from the claimed method because successful implementation of cell therapy and gene therapy protocols was not routinely achievable by those skilled in the art at the time of the invention. As noted above, in view of the present amendment to limit the claims to the *in vitro* embodiments, the issues of enablement have been reduced so that those issues pertaining exclusively to the *in vivo* embodiments have been eliminated from the rejection. Thus, a number of the references cited in the rejection of record are no longer cited in the present rejection. However, the pending claims remain directed to methods that involve the transfection of human

embryonic stem cells and human hematopoietic stem cells and the enablement rejection regarding these aspects is maintained.

At page 9 of the response, Applicants point to the 37 CFR 1.132 Declaration of Dr. Lipton filed on August 29, 2008 for describing the transfection of human embryonic stem cells with a lentivirus-MEF2CA construct. The Declaration states that a nestin enhancer was used to regulate expression of a construct encoding a constitutively active form of MEF2C, designated MEF2CA, and that when murine embryonic stem (ES) cells were stably transformed with this construct, the ES cells differentiated into a virtually pure population of neurons. The Declaration presents data relating to the effect of MEF2C expression in human ES cells on neurogenesis. The human ES cells were transfected with a lentivirus encoding a constitutively active form of MEF2C. The origin of the lentivirus is not described and therefore it is unclear if the lentivirus used in the transfection studies is a mouse lentivirus or perhaps a human lentivirus. Nevertheless, while the Declaration provides considerable specific guidance with regard to the transfection of human embryonic stem cells, the as-filed specification provides no specific guidance for transfecting human ES cells. The courts have held that sufficiency under 35 U.S.C. 112 must be judged as of the filing date. If a disclosure is insufficient as of the time it is filed, it cannot be made sufficient, while application is pending, by later publications which add to knowledge of the art so that the disclosure, supplemented by such publications, would suffice to enable the practice of the invention. If information to be found only in subsequent publications is needed for such enablement, it cannot be said that the application disclosure evidences a completed invention. *In re Glass*, 181 USPQ 31 (CCPA 1974).

At page 9 of the response, Applicants allege that one of ordinary skill in the art would know methods for contacting *in vitro* progenitor cells with a differentiating agent as set forth in the claims. Applicants point to the previous Office action at page 10 (action mailed 3/18/09) for stating that "…much work has been done to develop techniques for the directed differentiation of ES cells *in vitro* to produce

desired cell types…" However, the scope of the claim term "progenitor cells" is not limited to ES cells, but instead is extremely broad, covering every stem cell and precursor cell type from any species and the differentiating agent is broadly recited to cover any factor. Therefore, the various possible combinations of progenitor cells and differentiating agents is extremely large, with no specific guidance on the direction in which experimentation should proceed. While a scope of enablement is acknowledged for the use of **mouse** ES cells in the method, methods for the directed differentiation of **human** ES cells were not known in the art at the time of the instant invention. Contrary to Applicants' assertion that one of ordinary skill in the art would know methods for contacting *in vitro* progenitor cells with a differentiating agent as set forth in the claims, and in direct rebuttal of this assertion, at the time of the instant invention, Pera et al. (2000, J. Cell Sci. 113: 5-10) reported that "[a]t present, no one has reported large scale growth, efficient cloning or genetic manipulation of human ES or EG cells" and "[d]irected differentiation of human ES cells into specific lineages has not yet been achieved" (page 9, colum 2, paragraph 2).

At page 9 of the response, Applicants assert that Rossi and Cattaneo, Cao et al., Mehler et al., and Cheng et al. do not apply to the claimed methods of introducing *in vitro* into progenitor cells a nucleic acid molecule because the arguments presented by the Office, which the references support, are related to enablement for *in vivo* methods. At page 10 of the response, Applicants likewise contend that Jackowski, Grados-Munro et al., and Filbin are not relevant to the presently claimed methods directed to methods of differentiating progenitor cells *in vitro* to produce a cell population containing neuronal cells protected from apoptotic cell death. In response, first, Cheng et al. was not cited in the rejection of record. Second, it is agreed that the remaining references pertain primarily to enablement for *in vivo* embodiments, which have now been cancelled from the claims. As noted above, in view of the present amendment to limit the claims to the *in vitro* embodiments, the issues of enablement have been reduced so that those issues pertaining exclusively to the *in vivo* embodiments have been eliminated from the rejection. Thus, a

number of the references cited in the rejection of record are no longer cited in the present rejection. However, the pending claims remain directed to methods that require the transfection of human embryonic stem cells and human hematopoietic stem cells and the enablement rejection regarding these aspects is maintained.

At page 10 of the response, Applicants reiterate their arguments of record regarding Hanazono et al. and Zwaka and Thomson with respect to their disclosure of introducing *in vitro* nucleic acids into human hematopoietic stem cells, particularly in view of the disclosures of Eiges et al., Ferrari et al., and Uyttersprot et al. Applicants assert that Hanazono et al. describes the use of retroviral vectors and lentiviral vectors for gene transfer into human hematopoietic stem cells and Eiges et al. describes the successful transduction of human ES cells using routine methods well known to those skilled in the art at the time of filing the priority application. However, methods for successfully transducing human ES cells were not known at the time of filing the priority application and the instant specification provides no specific guidance with regard to the genetic modification of human ES cells. Zwaka et al. (2003) was first cited by the Examiner in the rejection of record in the Office Action of 11/28/03 for documenting the difficulties encountered in attempting to transfect human ES cells. Zwaka et al. is a post-filing reference that describes an improved electroporation method that was specially adapted for human ES cells and the instant specification does not provide specific guidance for using electroporation techniques for transfecting human ES cells. With regard to embryonic stem cells in general, the specification provides only a laundry list of techniques that could be used to introduce a nucleic acid molecule into an embryonic stem cell. With regard to human ES cells specifically, no specific guidance for their genetic modification is provided. When take as a whole, in combination with the limited guidance of the specification and other unpredictabilities in the art of directed differentiation, the lack of a known and available transfection method for human ES cells is clearly an additional obstacle that must be overcome to enable the claimed invention which is very broad in terms of the types of progenitor cells and stem

cells that can be used in carrying out the claimed method. The instant specification provides no specific guidance with regard to the genetic modification of human ES cells and does not mention either FUGENE or ExGen 500 transfection reagents as being particularly suitable for the genetic modification of human ES cells. Ferrari et al. (1997) and Uyttersprot et al. (1998) likewise do not suggest using FUGENE or ExGen 500 for the genetic modification of human ES cells. Ferrari et al. teaches the transfection of lung epithelial cells by a chemical transfection method that uses ExGen 500. Uyttersprot et al. teaches the transfection of dog and human thyrocytes by a chemical transfection method that uses the transfection reagent FUGENE. Thus, at time of filing the priority application, neither the specification nor the prior art disclosed a method for the genetic modification of human ES cells and the specification did not provide specific guidance with regard to the genetic modification of human ES cells. Thus, at the time of filing, methods for successfully transfecting human ES cells were not known. This is a factor that must be taken into consideration when evaluating enablement across the full scope of the claims. When considered in combination with the other factors confounding the transduction of human hematopoietic stem cells, the conclusion is that undue experimentation would have been required to practice the claimed invention across the full scope.

At page 11, paragraph 1 of the response, Applicants cite van Hennik et al. (1998) for showing the highly efficient transduction of human umbilical cord stem cells with a green fluorescent protein gene using a retroviral vector. In particular, Applicants submit that van Hennik et al. describes that Moloney murine leukemia virus (MoMLV) can be used to transduce human hematopoietic cells. However, the instant specification does not mention Moloney murine leukemia virus (MoMLV) at all, let alone provide specific guidance for using it to transduce human hematopoietic stem cells or the particular human hematopoietic progenitor cell populations recited in Claims 91-95.

At page 11, paragraph 2 of the response, Applicants point to the Declaration of Dr. Stuart Lipton filed August 29, 2008, which includes data regarding transfection of human embryonic stem cells with

MEF2CA. Applicants note that Exhibit B provides data showing the neurogenic activity of MEF2CA in human embryonic stem cells. However, the instant specification does not provide specific guidance for using a lentivirus to transduce human embryonic stem cells. As discussed above, although the Declaration discloses that the human ES cells were transfected with a lentivirus encoding a constitutively active form of MEF2C, the origin and type of lentivirus is not described and therefore it is unclear if the lentivirus used in the transfection studies is a mouse lentivirus or perhaps a human lentivirus. Nevertheless, while the Declaration provides considerable specific guidance with regard to the transfection of human embryonic stem cells, the as-filed specification provides no specific guidance for transfecting human ES cells. The courts have held that sufficiency under 35 U.S.C. 112 must be judged as of the filing date. If a disclosure is insufficient as of the time it is filed, it cannot be made sufficient, while application is pending, by later publications which add to knowledge of the art so that the disclosure, supplemented by such publications, would suffice to enable the practice of the invention. If information to be found only in subsequent publications is needed for such enablement, it cannot be said that the application disclosure evidences a completed invention. *In re Glass*, 181 USPQ 31 (CCPA 1974).

At page 11, paragraph 3 of the response, Applicants point to the teachings of the specification on pages 54-55, for describing a variety of methods known in the art for introducing a nucleic acid into a progenitor cell *in vitro*. With regard to human hematopoietic stem cells (HSCs) and human embryonic stem cells, however, the guidance is in the form of general guidance rather than the **specific** guidance that is needed.

At page 11, paragraph 4 of the response, Applicants assert that not only does Hanazono et al. support Applicants' position that viral vectors were routinely used for gene transfer into hematopoietic stem cells, but van Hennik et al. as well corroborates the routine use of viral vectors to transduce human hematopoietic stem cells *in vitro*. The teachings of van Hennik et al. have already been addressed herein

above. In addition, contrary to Applicants' assertion, instead of corroborating the routine use of viral vectors to transduce human hematopoietic stem cells *in vitro*, van Hennik et al. acknowledge the considerable difficulty encountered in trying to transfer genes into **human** HSCs, stating that "[r]etroviral-mediated gene transfer to [human immature hematopoietic cells with repopulating capacity], which is attractive by its simplicity and efficiency, has, however met with considerable difficulty, which is only partly understood" (page 4013, column 1, paragraph 1). The reference goes on to say that "[t]he efficiency of gene transfer to stem cells is limited by the inability of most retroviral vectors to integrate DNA into the cellular genome of quiescent cells" (sentence bridging pages 4013-4014). With regard to Hanazono et al. (2001), contrary to Applicants' contention that the reference supports Applicants' position that viral vectors were routinely used for gene transfer into hematopoietic stem cells, Hanazono et al. state that "the gene transfer efficiency into human HSCs with retroviral vectors was very low in contrast to the much higher efficiency observed in murine experiments" and that "[t]he more quiescent nature of human HSCs and the lower density of retroviral receptors on them hindered the efficient gene transfer with retroviral vectors" (abstract). Thus, Hanazono et al. (2001) clearly acknowledged that gene transfer into human hematopoietic stem cells was problematic at the time of the invention.

At page 11, paragraph 4 of the response, Applicants further assert that the evidence provided in the August 29, 2008 Declaration of Dr. Lipton corroborates Applicant's position that the specification provides sufficient description and guidance to enable the claimed methods. As discussed above, while the Declaration provides considerable specific guidance with regard to the transfection of human embryonic stem cells, the as-filed specification provides no specific guidance for transfecting human ES cells. The courts have held that sufficiency under 35 U.S.C. 112 must be judged as of the filing date. If a disclosure is insufficient as of the time it is filed, it cannot be made sufficient, while application is pending, by later publications which add to knowledge of the art so that the disclosure, supplemented by such publications, would suffice to enable the practice of the invention. If information to be found only in

subsequent publications is needed for such enablement, it cannot be said that the application disclosure evidences a completed invention. *In re Glass*, 181 USPQ 31 (CCPA 1974).

At page 12 of the response, Applicants refer to the prior Office action at page 5, page 19, and page 17 for arguments pertaining to *in vivo* embodiments, which have now been deleted from the claims. Accordingly, the arguments pertaining to the *in vivo* embodiments have been withdrawn.

At page 13 of the response, Applicants conclude that the specification contains a teaching of the manner and process of making and using the invention and that the Office has provided no reason to doubt the objective truth of the statements contained therein. On the contrary, it is maintained that the arguments and references cited in the rejection provide specific reasons for doubting that one skilled in the art could transduce human hematopoietic stem cells and human ES cells without undue experimentation.

Accordingly, it is maintained that claims limited to

a method of differentiating progenitor cells *in vitro*, comprising the steps of (a) contacting *in vitro* said progenitor cells with **retinoic acid**; and (b) introducing *in vitro* into said progenitor cells a nucleic acid molecule encoding a constitutively active MEF2C polypeptide, wherein said progenitor cell is selected from the group consisting of a P19 cell and a mouse embryonic stem cell, thereby differentiating said progenitor cells to produce a cell population containing neuronal cells protected from apoptotic cell death,

would be appropriate.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 80-99 stand rejected under 35 U.S.C. 102(a) as being anticipated by Okamoto et al. (2000, Proc. Natl. Acad. Sci. 97(13): 7561-7566, published online June 13, 2000).

The claims are directed to a method of differentiating progenitor cells by (a) contacting said progenitor cells with a differentiating agent, and (b) introducing into said progenitor cells a nucleic acid molecule encoding a MEF2 polypeptide or an active fragment thereof, thereby differentiating said progenitor cells to produce a cell population containing protected neuronal cells.

Okamoto et al. (2000) discloses P19 cells treated with retinoic acid and subsequently transfected with a plasmid encoding a constitutively active form of MEF2C (page 7563, column 1, paragraph 2). The reference further discloses that transfection of P19 cells with an expression vector encoding a dominant negative form of p38α resulted in enhanced apoptotic cell death in differentiating cells (page 7565, column 2, paragraph 2). Coexpression of constitutively active MEF2C rescued the differentiating cells from apoptosis (Figure 5B and page 7565, column 2, paragraph 2). The authors conclude that the p38α/MEF2 cascade plays a role in preventing apoptotic cell death during neuronal differentiation. The neurons expressing constitutively active MEF2 represent a population of protected neuronal cells, as presently claimed.

Thus, the claimed invention is disclosed in the prior art.

At pages 13-14 of the response, Applicants point out that the priority application was filed June 5, 2000. Accordingly, Applicants allege that the priority date of the subject application is prior to the publication date of Okamoto et al. based on the arguments of record and the enablement arguments presented. However, the present claims are not entitled to the priority date of June 5, 2000 for the reasons discussed above with regard to priority. The present application fails to provide an enabling disclosure for the present claims for the reasons discussed hereinabove. Likewise, the priority application fails to

provide an enabling disclosure. Accordingly, the Okamoto et al. is properly applied under 35 U.S.C. 102(a) and the rejection stands or falls with the enablement rejection.

Claims 80, 81, 85, and 96-99 stand rejected under 35 U.S.C. 102(b) as being anticipated by Krainc et al. (1998, J. Biol. Chem. 273(40): 26218-26224).

The claims are directed to a method of differentiating progenitor cells *in vitro* to produce a cell population containing neuronal cells protected from apoptotic cell death, comprising the steps of (a) contacting *in vitro* said progenitor cells with a differentiating agent; and (b) introducing *in vitro* into said progenitor cells a nucleic acid molecule encoding a constitutively active MEF2 polypeptide or an active fragment thereof, thereby differentiating said progenitor cells *in vitro* to produce a cell population containing neuronal cells protected from apoptotic cell death.

Krainc et al. (1998) disclose that the plasmid pG/DN, containing the N-terminal DNA binding domain of MEF2C, was stably transfected into P19 cells (Figure 5 and page 26219, column 1, paragraph 4 and page 26222, column 2, paragraph 2). The reference notes that these cells differentiate into a neuronal phenotype after treatment with retinoic acid, and then express MEF2C (page 26222, column 2, paragraph 2).

Thus, the claimed invention is disclosed in the prior art.

At page 15 of the response, Applicants allege that Krainc et al. provides no teaching of introducing into progenitor cells a nucleic acid molecule encoding a constitutively active MEF2 polypeptide or an active fragment thereof to produce a cell population containing neuronal cells protected from apoptotic cell death. Applicants note that Krainc et al. describes a construct encoding a dominant-negative MEF2C. Citing Krainc et al. at page 26222, column 2, paragraph 2, Applicants allege that, when introduced into P19 cells, the dominant-negative MEF2C "totally abolished the cells from differentiating into a neuronal phenotype following treatment with retinoic acid" (response at page 15, paragraph 2). On

the contrary, however, the reference does not say or even suggest that differentiation into the neuronal phenotype was abolished, but instead actually says that "induction of NR1 mRNA expression ….was totally abolished … in P19 cells stably expressing the dominant-negative MEF2C (Fig. 5A, lane 5)" (page 26222, column 2, paragraph 2). The same paragraph clearly states that these P19 cells "differentiate into a **neuronal** phenotype after treatment with 13-*cis*-retinoic acid, **and then** express MEF2C" (emphasis added). Thus, it is made clear that P19 cells treated with 13-*cis*-retinoic acid, first differentiate into a neuronal phenotype and **then** express MEF2C. Accordingly, while expression of the dominant-negative form of MEF2C abolished induction of NR1 mRNA expression, it did not abolish differentiation into the neuronal phenotype. Applicants seem to be contrasting the claim language, directed to the use of a "constitutively active MEF2 polypeptide or an active fragment thereof," with the experiments of Krainc et al. that involved the expression of a dominant-negative form of MEF2C. While Applicants have not suggested that the dominant-negative form of MEF2C does not meet the claim limitation directed to the use of a "constitutively active MEF2 polypeptide or an active fragment thereof," it is nevertheless noted that the N-terminal fragment of MEF2C used in the experiments of Krainc et al. contains the entire DNA-binding domain of the MEF2C protein and therefore is **both** constitutively active for DNA binding and an active fragment of a MEF2 polypeptide, as set forth in the claims. Therefore, Krainc et al. clearly teaches "introducing *in vitro* into said progenitor cells a nucleic acid molecule encoding a constitutively active MEF2 polypeptide or an active fragment thereof" as instantly claimed. Furthermore, with regard to the functional language of producing "a cell population containing neuronal cells protected from apoptotic cell death," Applicants are reminded that it is well established that when the structure recited in the reference is substantially identical to that of the claims, claimed properties or functions are presumed to be inherent. See MPEP 2112.01 and *In re Best,* 195 USPQ 430, 433 (CCPA 1977). Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a *prima facie* case of either anticipation or obviousness

has been established. *In re Best*, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." The office does not have the facilities for examining and comparing applicant's product with the product of the prior art in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed products are functionally different than those taught by the prior art and to establish patentable differences. See *Ex parte Phillips*, 28 USPQ 1302, 1303 (BPAI 1993), *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray*, 10 USPQ2d 1922, 1923 (BPAI 1989). In the instant case, there is no evidence demonstrating that the MEF2C-transfected P19 progenitor cells of Krainc et al. are functionally different from those recited in the claims. The neurons disclosed therein were produced using the same method as that claimed and therefore must necessarily be "protected from apoptotic cell death" as claimed.

Conclusion

No claims are allowable.

All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing

date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne-Marie Falk whose telephone number is (571) 272-0728. The examiner can normally be reached Monday through Friday from 9:00 AM to 5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras, can be reached on (571) 272-4517. The central official fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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/Anne-Marie Falk/
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